REMARKS

Information Disclosure Statement

A Supplemental Information Disclosure Statement (IDS) was mailed on October 27, 2004 (received by the U.S. Patent & Trademark Office on November 1, 2004). Entry of the Supplemental IDS is respectfully requested. Because a Request for Continued Examination was filed on February 11, 2004 and the following Office Action was mailed on November 2, 2004, it is believed that no fee is required.

Claim Amendments

Claims 1 has been amended. Claims 43 and 44 have been added.

Claim 1 has been amended to include the recitation "of a molecule", in order to further clarify the claimed subject matter. The recitation "of a target molecule" was deleted in the prior Amendment.

New Claim 43 recites that the molecule is a nucleic acid polymer, and new Claim 44 recites that the nucleic acid polymer is an oligonucleotide. Support for the new claims can be found, for example, in Examples 1 and 2.

No new matter has been added.

Rejection of Claims 1-3, 6, 7, 9 and 12 Under 35 U.S.C. § 112, Second Paragraph

Claims 1-3, 6, 7, 9 and 12 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention.

A. Claim 9

The Examiner states that it is not clear how the use of phosphoramidites result in the formation of phosphate. The Examiner further states that "all the instant claims require is [the] addition of phosphoramidate as a terminal group to an unprotected nucleotide."

Applicants respectfully disagree that it is unclear how phosphoramidites are used in a process that results in the formation of a phosphate group. As evidence, Applicants are attaching hereto pages 1141-1144 of Organic Chemistry, 3rd Edition, by John McMurry (1992) as "Exhibit A". On page 1143, step 3, the reaction of a phosphoramidite moiety with a hydroxyl moiety is shown, which produces a phosphite ester. In step 4 (page 1144), the phosphite ester is oxidized to a phosphate ester with iodine. The phosphate ester is converted to a phosphate residue in step 5 (page 1144) by reacting the phosphate ester with ammonia in the presence of water.

Exhibit A thus demonstrates that phosphoramidite chemistry, in the context of nucleic acids, was well-known prior to the effective filing date of the instant application (indeed, more than 5 years prior to the effective filing date). Because at least one series of reactions progressing from phosphoramidite addition to phosphate formation was known to one of ordinary skill in the art, the claim is definite by virtue of reciting the initial step (phosphoramidite addition) and the final product (a phosphate residue). One of ordinary skill in the art would have been immediately able to fill in the intervening steps and the conditions appropriate for formation of a phosphate residue based upon his or her knowledge of the art, and therefore the claim clearly defines the claimed subject matter.

In Claim 6, in step 2, the activated sites are reacted with one or more compounds that ***directly or indirectly*** result in a negatively charged phosphate residue becoming bound to at least one of *i*) the plurality of oligonucleotides and *ii*) the plurality of protected regions. In other words, the "comprising" language of the claim allows the phosphate residue to be produced through other, unrecited steps that are known to one of ordinary skill in the art. Reacting the activated sites with the compounds is ***not*** required to produce the phosphate residue in a single step. Instead, the claim allows for multiple steps to obtain the phosphate residue, as is the case with a phosphoramidite. Because one of ordinary skill in the art would have known which reactions to use in conjunction with a phosphoramidite to produce a phosphate residue, the claim is clear in terms of how to obtain a phosphate residue.

It is noted that the test for definiteness is provided by MPEP § 2173.02, which states: "The essential inquiry pertaining to this requirement is whether the claims set out and

circumscribe a particular subject matter with a reasonable degree of clarity and particularity. Definiteness of claim language must be analyzed, not in a vacuum, but in light of:

(A) The content of the particular application disclosure;

(B) The teachings of the prior art; and

(C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made." As discussed above and shown in Exhibit A, the teachings of the prior art are extensive, such that reference to the use of a phosphoramidite in forming a phosphate residue is sufficient for clarity of the claims.

B. Claim 1

Claim 1 has been amended to restore the recitation of a "molecule". Thus, it has been further clarified that the claimed method reduces non-specific binding of molecules to an oligonucleotide array.

C. Claim 1

Step b) ii) of Claim 1 has been amended to recite "said molecule", which finds antecedent basis in the preamble.

In summary, the claims particularly point out and distinctly claim the presently-claimed aspects of the invention. Because it was well known how to obtain a phosphate residue based upon an initial reaction with a phosphoramidite, the claims are definite, even without explicitly reciting each step in the synthetic pathway. It is sufficient to recite that the method ***comprises*** reaction with a phosphoramidite. The issues regarding "target molecules" have been addressed by amendments. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-3, 6, 7, 9 and 12 Under 35 U.S.C. § 112, First Paragraph

Claims 1-3, 6, 7, 9 and 12 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled by the specification.

In the first aspect of the rejection, the Examiner states that there is no showing of how to deliver a negatively charged phosphate group by reacting an activated site with a phosphoramidite of formula (II). As shown in Steps 3, 4 and 5 of Exhibit A, it was well known as of the effective filing date that reaction with a phosphoramidite, followed by several conventional reactions (oxidation of a phosphite ester to a phosphate ester and hydrolysis of the phosphate ester to phosphate), results in the formation of a phosphate residue. Because synthesis of a phosphate residue from a phosphoramidite starting material was well known as of the effective filing date, there is no need for the specification to describe this transformation.

In the second aspect of the rejection, the Examiner states that the specification does not provide support for the claimed effect of reducing non-specific binding by introducing negatively-charged phosphate groups. Applicants respectfully disagree.

In vivo, nucleic acids exist as a string of point charges, which are provided by negatively-charged phosphate groups. ***Because an organism depends on nucleic acids interacting specifically with other nucleic acids and proteins, for example, the presence of a multiplicity of negative charges clearly must not interfere with the specificity of these interactions.*** Moreover, these negative charges generally extend for thousands of bases beyond the specifically-interacting region of a nucleic acid. For this reason, the issues raised by the Examiner find no scientific basis. Because non-specific binding would interfere with *in vivo* biological function, the presence of additional negative charges outside of a probe sequence must not significantly increase non-specific binding to that sequence.

The data shown in Tables 1 and 2 of the Examples support this reasoning. In Table 1, the signal/noise ratio for various test sequences is shown when "C3" or "HEX" groups are added. The C3 group is $-PO_2^{(-)}O(CH_2)_3O-$ and the HEX group is $-PO_2^{(-)}O(CH_2CH_2O)_6-$. Obviously, both of these groups include a negatively-charged phosphate group. Adding one or both of the groups between a substrate and a probe sequence improves the signal/noise ratio in the assay. The increase in the signal/noise ratio reflects a decrease in non-specific binding as additional negatively-charged phosphate groups are added.

In Table 2, the results of varying the number of C3 groups and removing a protecting group from a probe sequence are shown. When the protecting group, MeNPOC, is removed, a

free hydroxyl group is left in its place (see page 45, lines 1-14). As in Table 1, the signal/noise ratios increased as the number of negatively-charged C3 groups increased. In addition, removal of the protecting group significantly decreased the specular background (due to insoluble particulates such as fine precipitates of metal hydroxides, see page 40, line 30 to page 41, line 2) and improved the signal/noise ratio by about 9%. Because removal of a protecting group and addition of negatively-charged phosphate groups separately decreased non-specific binding to arrays, it is expected that both removing protecting groups and adding negatively-charged phosphate groups would also decrease non-specific binding to an array.

The Examiner is incorrect in stating that the examples only demonstrate reduction of binding of a phycoeretrin-strepavidin protein complex. As discussed above, at least Example 2 also demonstrates reduction in binding of other fluorescent materials, such as metal hydroxyide particulates. Moreover, as discussed at page 43, lines 1-6, the phycoeretrin-strepavidin protein complex is simply a stain used to quantify the binding (specific and non-specific) of a biotinylated oligonucleotide target. Based on the fact that the examples demonstrate a reduction in non-specific binding of a nucleic acid target as well as metal hydroxides, one would expect that the disclosed method would decrease non-specific binding to other oligonucleotide probes.

It is further emphasized that the Examiner has provided no reasoning to explain why the multitude of negative charges from phosphate residues *in vivo* would increase non-specific binding. Clearly, the extensive negative charge of nucleic acids *in vivo* does not increase non-specific binding; otherwise, an organism would not be able to exist. Nevertheless, Applicants point out the new Claims 43 and 44 are directed to nucleic acids and oligonucleotides, respectively, both of which are negatively-charged. Thus, the Examiner's arguments regarding positively-charged molecules are not applicable to these claims.

In summary, Claims 1-3, 6, 7, 9 and 12 are fully enabled by the specification. Furthermore, new Claims 43 and 44 are clearly enabled by the specification. Nucleic acids are negatively-charged molecules. As demonstrated in Examples 1 and 2, the addition of further negatively-charged phosphate residues does not increase non-specific binding, but instead significantly decreases such non-specific binding. In addition, removal of protecting groups, which are typically hydrophobic (e.g., MeNPOC), also reduces non-specific binding. Thus, the

claimed method clearly reduces non-specific binding associated with hydrophobic interactions and does not increase non-specific binding associated with electrostatic attraction (because the nucleic acid probes in an array are negatively charged prior to adding phosphate residues, the array simply maintains a negative charged when modified in this manner). Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 6, 7 and 9 Under 35 U.S.C. § 112, First Paragraph

Claims 6, 7 and 9 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly not being described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed. The Examiner states that Claim 6 introduces new matter with the phrase "one or more compounds."

In the discussion of adding a negatively-charged phosphate residue in Example 1, it is disclosed that this addition involves reaction with a phosphoramidite and standard coupling/deprotection protocols. Based on this disclosure, the instant application clearly contemplates the use of one or more compounds, one of which is a source of phosphorus, in forming a phosphate residue. Thus, the recitation "one or more compounds" is supported in the application as originally filed. Reconsideration and withdrawal of the rejection are respectfully requested.

In view of the above amendments and remarks, Applicants believe the pending application is in condition for allowance.

Applicants believe no fee is due with this response, aside from the fee associated with the Petition for Extension of Time. However, if an additional fee is due, please charge our Deposit Account No. 18-1945, from which the undersigned is authorized to draw, under Order No. AFMX-P02-038.

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Respectfully submitted,

By _____

Jesse A. Fecker
Registration No.: 52,883
ROPES & GRAY LLP
One International Place
Boston, Massachusetts 02110-2624
(617) 951-7000
(617) 951-7050 (Fax)
Attorneys/Agents For Applicant